Literature Search on Animal Aggression Induction via Anti-Anxiety Medication

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9/6/14

My literature search has found relatively little to suggest that use of SSRIs (such as Fluoxetine) are likely to cause an increase in aggression, and SSRIs/TCAs are used to decrease aggression at least as well as placebos.

Several studies looking at the use of SSRIs or other anti-depressants in dogs for behavioral problems (including aggression) show an improvement in behavior equal to or greater than the improvement from placebo. Importantly, these studies often note that there is no increase in aggression after initiating medication, and one veterinarian/researcher noted via blog that he has seen no cases of increased aggression due to Fluoxetine use in over 25 years of practice. Consistent with these canine studies, research in dominant queens of naked mole rat colonies show decreased aggression after Fluoxetine administration. Due to its efficacy and its relatively minor side effects, Dr. Karen Pryor specifically recommends Fluoxetine (SSRI) for outburst aggression/related issues and makes no mention of increased aggression, although she does suggest a rare side effect may be frantic behavior. Importantly, a study in rats suggested that use of TCAs (sometimes used for aggression instead of SSRIs) does not affect impulse control after same-day administration.

Human studies looked very similar. Use of Fluoxetine in patients with intermittent explosive disorder caused significant reductions in impulsive aggressive behavior, although the drug was only effective in about 50% of patients. There was no mention of increased aggression. In addition, a meta-analysis found no link between Fluoxetine use in children/adolescents and aggression. This is not to say that individuals may not react contrary to the average, but the studies made no specific mention of individual divergent reactions. Interestingly, another literature review noted that two studies did show an increase in anger in 4-7% of humans with depression who were treated with SSRIs; however, 20% of depressed humans left untreated eventually showed anger, suggesting that SSRI use might actually decrease anger development in this group.

Now, there are some studies that suggested that some animals might have increased aggression from either short- or long-term use of anti-anxiety meds. One dog study used a Benzodiazepine for the first 4 weeks (which research suggests can increase aggression), then Fluoxetine thereafter. The study found that, of 4 “dominant-aggressive” dogs, 1 became worse on drugs and the 1 food-aggressive dog also showed a behavioral declines; in total, the group found 3 of 12 (25%) aggressive dogs showed an increase in aggression. However, because there was no control group, we cannot know how many dogs would have become worse in the absence of the drug, making it difficult to determine whether the drugs were the cause. Interestingly, studies in Golden Hamsters suggest that use of SSRIs might increase aggression depending on the age and dose at which the drug is administered. In adults, Fluoxetine decreases aggression, whereas, high Fluoxetine doses in juveniles decrease aggression and low doses increase aggression.
Interestingly, I did find a study from a respectable fear lab that found that acute SSRI use (single-dose of Fluoxetine) increases fear learning, but long-term use reduces fear learning.\textsuperscript{14} We could interpret this to mean that animals could be more susceptible to fear-learning during the first few days/weeks of SSRI use, and that families should possibly be careful during this time use to avoid fear-inducing situations. Not really relevant here, but of possible future fear/aggression interest.

Based on these studies, there does not appear to be compelling evidence that a dog will experience increased aggression due to common (non-benzodiazepine) anti-anxiety medication use, as medication causes most dogs’ aggressive behavior to improve. The belief that dogs will become more aggressive on non-benzo anti-anxiety medication does not appear to be founded on current research, and may instead stem from studies on benzodiazepines or human suicide rates with SSRI use, the likely cause of which is mechanistically dissimilar to canine aggression. However, each dog is an individual, and if use does result in the unlikely increase in aggression, then medication can be stopped and other medications used instead. As always, behavioral modification must be used in conjunction with medication in order to see progress.

\textbf{Bibliography}

1. 34 dogs (15 of which were aggressive) improved or stayed the same on drugs. No placebo control. “There were no reports of worsened cases or serious side effects.”

2. 3 weeks of Fluoxetine treatment in 22 aggressive dogs results in “all owners reporting an improvement of the problem.”

3. 28 dogs over 1 yo treated for dominance aggression with Clomipramine and behavior modification; showed improvement, but no better than placebo. No mention of worsening.
   Note: Clomipramine is TCA and not SSRI.

4. Reduced aggression in 12mo old dog was dependent upon the use of Fluoxetine.

5. Fluoxetine effectively reduced aggression in small experimental group of dogs. In addition, first author has seen no cases of increased aggression on Fluoxetine in over 25 years of veterinary practice (see Dodman’s 04/04/13 article at Veterinary Practice News).

6. Decreased aggression in naked mole rat queens who are normally dominant and aggressive.
   \textit{Differential effects of chronic fluoxetine on the behavior of dominant and subordinate naked mole-rats}. Mongillo et al., (2014), Behav Brain Res.

7. For outburst aggression or related anxieties, use Fluoxetine. For social interaction anxieties, use Paroxetine. No mention of increased aggression, but possible rare side effect of frantic behavior.

9. Fluoxetine significantly reduced impulsive aggressive behavior in humans with intermittent explosive behavior (but only worked in ~50% of subjects.) *Note: Couldn’t access full article. A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder.* Coccaro et al., (2009), *J. Clinical Psychiatry.*


11. Performed literature review and found that possible increases in anxiety in some patients taking SSRIs, but data suggests overall reduced aggression. Two studies showed increased anger in 4-7% of Fluoxetine-treated humans with depression, which is actually lower than anger seen to emerge in placebo controls (20%). *Selective serotonin reuptake inhibitors and violence: a review of the available evidence.* Walsh & Dinan, (2009) *J. Clin Psychiatry.*

12. Of the 4 dogs who were “dominant aggressive,” 1 improved slightly, 2 did not improve, and 1 worsened. Of the 1 dog who was food aggressive, it was worse. Note: This study uses a benzodiazepine for the first 4 weeks of treatment, and other studies do suggest that Benzodiazepines can increase aggression. Saw no differences between juveniles and adults. *Fluoxetine combined with clorazepate dipotassium and behavior modification for treatment of anxiety-related disorders in dogs.* Pineda et al., (2014) *Vet J.*


14. I did find a study from a respectable fear lab that found that acute SSRI use (single-dose of Fluoxetine) caused an increase in fear learning, but long-term use reduced the ability for fear learning. This paper suggests that early use of SSRIs could cause animals to be more susceptible to fear-learning and that families should be careful during early days/weeks of SSRI use to avoid fear-inducing situations. *The selective serotonin reuptake inhibitor Citalopram increases fear after acute treatment but reduces fear with chronic treatment: a comparison with Tianeptine.* Burghardt et al., (2004) *Biol Psychiatry.*